Genetic and Health Determinants of Cancer Risk in Bangladeshi and Pakistani South Asians in the UK

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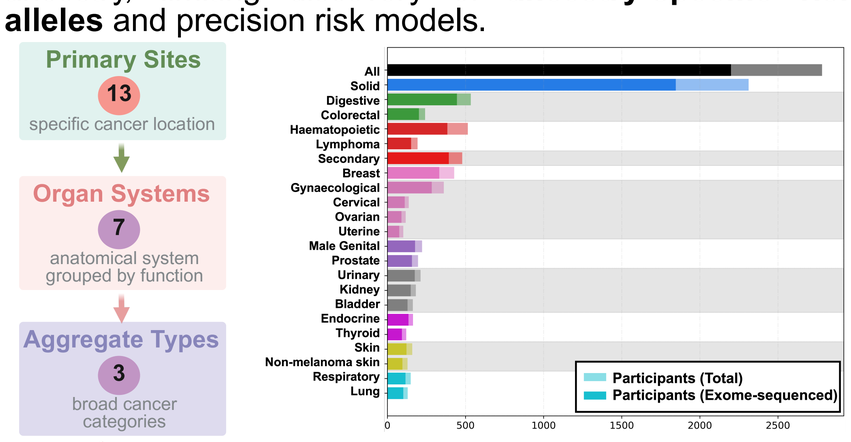
INTRODUCTION

Background

Cancer risk and outcomes vary by ancestry and environment.
South Asians are a rapidly growing population in the Western World but remain **underrepresented in healthcare research**.
Historically lower cancer incidence in South Asian migrants is **converging with host populations** with age and duration of residence.
Disproportionate diagnosis of cancer at **younger age and advanced stage.**
High prevalence of **type 2 diabetes, central obesity, metabolic syndrome, and chronic viral hepatitis**—key risk factors for multiple cancers with shared genetic susceptibility.

Knowledge gap

Less than 2% of GWAS participants are of South Asian ancestry, limiting discovery of **ancestry-specific risk alleles** and precision risk models.



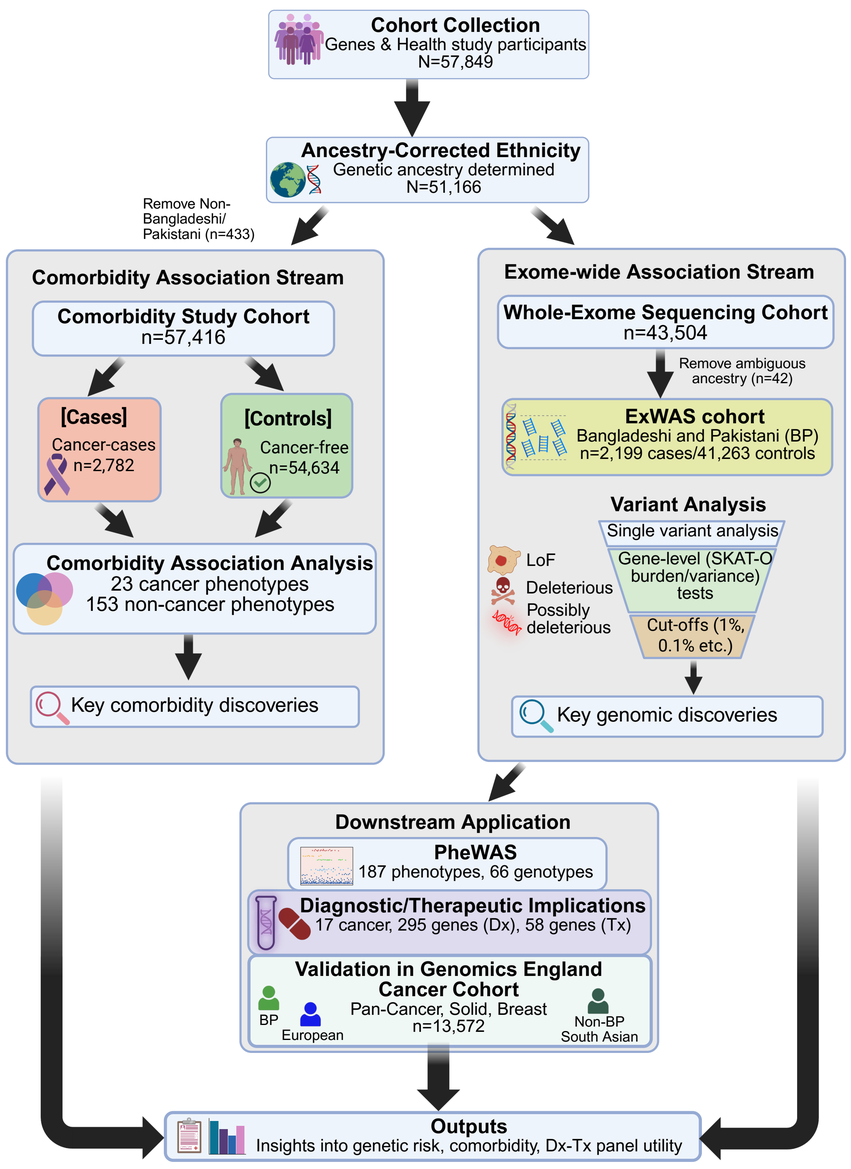
Objective

Using the **Genes & Health cohort** (~57,000 participants; ~2,800 cancer cases), we integrate **clinical phenotyping** and **whole-exome sequencing data of South Asian Bangladeshi and Pakistani (BP)** to define genetic and health determinants of cancer risk.

Impact

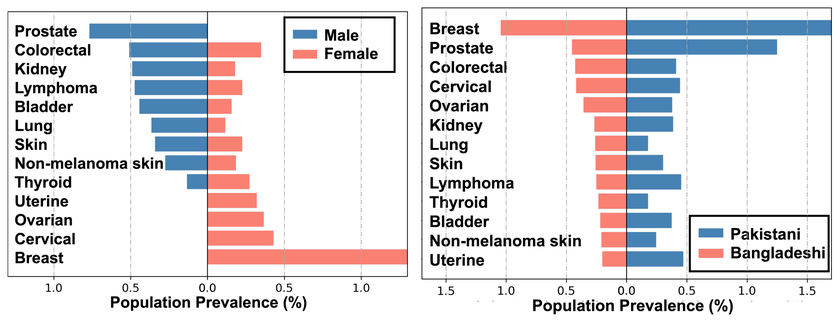
Advances equitable cancer genomics.
Enables population-specific risk stratification and biomarker discovery.
Informs precision prevention and screening strategies for South Asian populations.

ANALYTICAL WORKFLOW

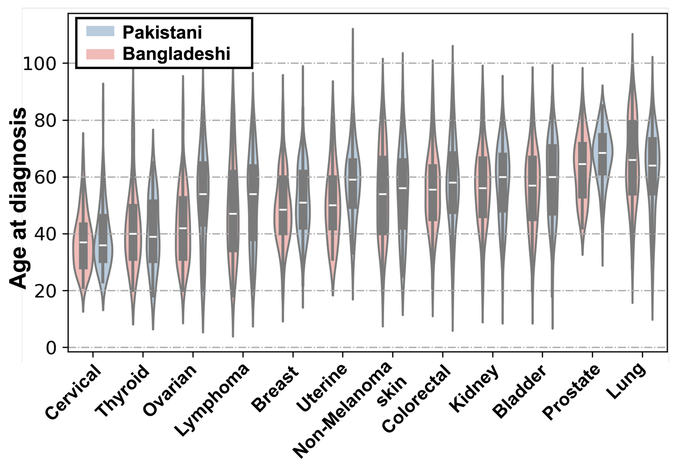


DEMOGRAPHICS

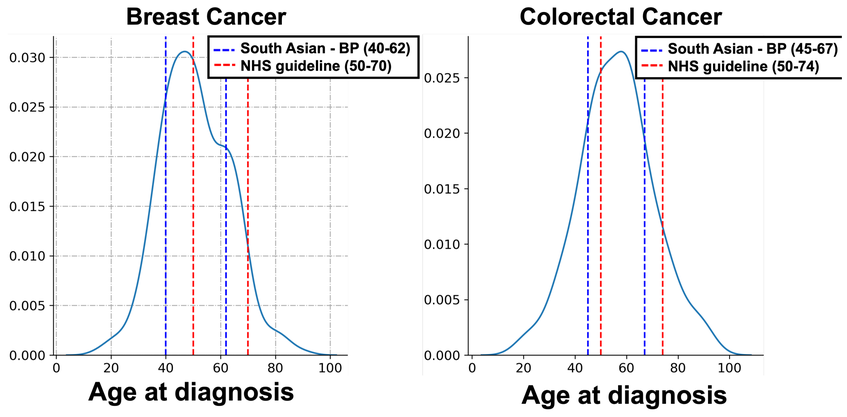
99% concordance between self-reported ethnicity and genetic ancestry; cohort comprised **52% Bangladeshi and 48% Pakistani** participants.
High rate of kinship, **61.5% participants are first cousins or closer**.



4.85% had a cancer diagnosis, with **gynaecological, digestive, and haematopoietic** cancers most prevalent; **breast, prostate, cervical, and colorectal** cancers were the most common primary sites.
Cancer incidence was **higher in men** (excluding sex-specific cancers), while **Pakistani participants had higher diagnosis** rates.



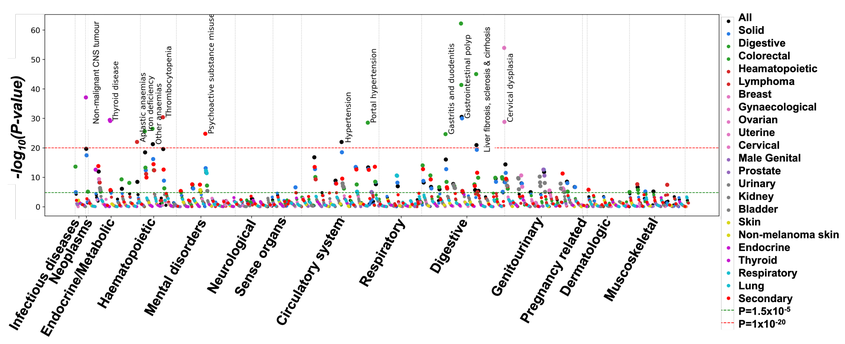
Bangladeshi participants were diagnosed **at younger ages** across multiple cancer types.
Median age of diagnosis was 51, substantially earlier than the general UK population.



Age-specific distributions suggest **earlier initiation of breast and colorectal cancer screening**, and a **narrower age window for cervical screening.**

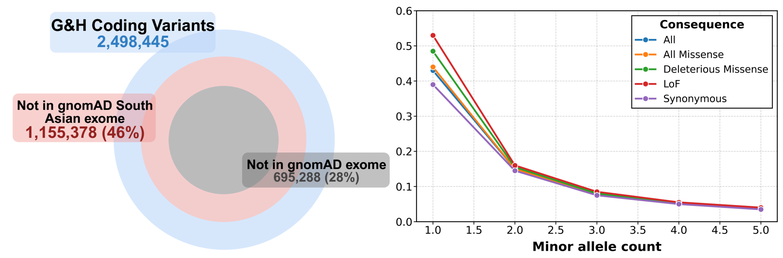
COMORBIDITY ASSOCIATION

147 significant cancer-morbidity associations identified after multiple-testing correction.
Male- and Bangladeshi-specific associations revealed in subgroup analyses, highlighting opportunities for targeted surveillance and risk stratification.

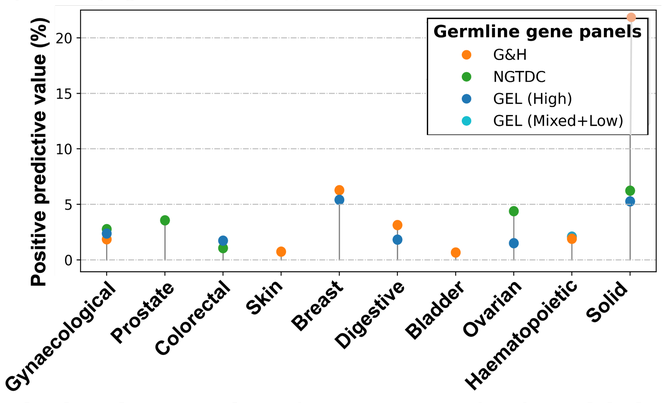


Largest effect sizes observed for **topographically concordant conditions**.
Systemic disorders are major contributors: obesity, hypertension, chronic kidney disease, and anaemias accounted for ~40% of associations, linking common cardiometabolic conditions to increased risk of digestive, haematological, and renal cancers.

EXOME-WIDE ASSOCIATION



43% singleton coding variants; a quarter of the variants were not seen before.
39 variant-level and 31 gene-level associations were identified, enriched for rare coding variations.
Over **60% novel -** no hit in OMIM, GWAS catalogue, AstraZeneca PheWAS (AZ-PheWAS), or FinnGen release 12 databases.
Notable loci included ***ARHGAP45*** (skin cancer), ***BRCA1*** (breast cancer), ***CBR1*** & ***NF1*** (solid cancer), ***FKBP6*** (lung cancer), and ***ZNF155*** (prostate cancer).
Nearly 70% of associations identified at the ancestry–subgroup level were unique to that subgroup.
Digestive system diseases had the highest proportion of **pleiotropic associations** with cancer-susceptibility genes (21%).



G&H-derived panels demonstrated the **highest PPV for 5 out of 10 cancers**.
Only 3 of 135 germline diagnostic panels from PanelApp and NGTDC demonstrated **5% PPV** in this cohort.
Out of the ExWAS-suggested 58 genes, **CGI database hit was 2 of 120** and **PharmGKB hit was 5 of 1,468**.

CONCLUSION

Key Findings

Largest genome–phenome cancer study of British South Asians: Integrated EHRs and exome sequencing in Bangladeshi and Pakistani populations revealed ancestry-specific cancer risk architecture.
Earlier cancer onset: Cancer diagnosis occurred substantially earlier than UK population benchmarks, particularly among Bangladeshi participants.
Distinct clinical risk patterns: Identified **147 cancer–comorbidity associations** and **70 genetic associations,** as well as many subgroup-specific associations undetectable in broader cohort.

Clinical & Translational Impact

Eurocentric models underperform: Screening guidelines, risk models, and gene panels show limited predictive value in South Asian populations.
Screening equity implications: Findings support earlier breast and colorectal screening and refined cervical screening windows for equitable NHS benefit.
Precision prevention opportunities: Links with modifiable conditions (e.g. obesity, hypertension) highlight actionable public health targets.
Need for ancestry-aware genomics: High-penetrance, ancestry-specific associations highlight the importance of substructure-aware analyses in genetically clustered populations.

ACKNOWLEDGEMENTS

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